

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 October 2001 (18.10.2001)

PCT

(10) International Publication Number
WO 01/76562 A1

- (51) International Patent Classification⁷: **A61K 9/16**, 9/52, 47/36
- (21) International Application Number: PCT/FI01/00322
- (22) International Filing Date: 3 April 2001 (03.04.2001)
- (25) Filing Language: Finnish
- (26) Publication Language: English
- (30) Priority Data:
20000780 3 April 2000 (03.04.2000) FI
- (71) Applicant (for all designated States except US): **NO-VASSO OY** [FI/FI]; Hermiankatu 8 D, FIN-33720 Tampere (FI).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **SÄKKINEN, Mia** [FI/FI]; Harjutie 5 F, FIN-03100 Nummela (FI). **MARVOLA, Martti** [FI/FI]; Elontie 24 as 3, FIN-00660 Helsinki (FI).
- (74) Agent: **TAMPEREEN PATENTTITOIMISTO OY**; Hermiankatu 6, FIN-33720 Tampere (FI).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 01/76562 A1

(54) Title: A PERORAL PHARMACEUTICAL FORMULATION FOR CONTROLLED RELEASE OF A DRUG

(57) Abstract: A peroral pharmaceutical formulation for controlled release of a drug contains a mixture of the drug and a polymer for controlling its release. The polymer is chitosan, particularly microcrystalline chitosan with a high crystallinity degree, and the mixture of the chitosan and the drug is in the form of granules or pellets. The preparation can be a dosage bag, a gelatine capsule or a compressed tablet containing the granules or pellets. The preparation can be best utilized in the administration of drugs which are only absorbed at the initial end of the gastrointestinal tract (e.g. furosemide) or which form undesirable metabolites when passed to the terminal end of the gastrointestinal tract, or which are susceptible of irritating the mucous membrane of the stomach (e.g. anti-inflammatory analgesics and corticoids).

A peroral pharmaceutical formulation for controlled release of a drug

Field of the invention

- 5 The invention relates to a peroral pharmaceutical formulation for controlled release of a drug, containing a mixture of the drug and a polymer for controlling its release.

Background of the invention

10

- Peroral pharmaceutical formulations, *i.e.* those to be taken orally, are developed for a large variety of drugs. The most important reason for the development has been to decrease the frequency of doses and/or to reduce adverse effects due to high peak contents of the drug. A large
15 number of techniques for producing peroral preparations with a long-term effect are known from patents and scientific references. It is characteristic of them that the release of the drug is controlled by a polymer. The preparation can be either 1) of a matrix type, wherein the diffusion of the drug from the matrix and/or the erosion of the matrix is the
20 mechanism controlling the release, or 2) a preparation with a film coating, wherein the diffusion of the drug through pores in the polymer film or a hole made therein is the mechanism controlling the release. Each of the above-mentioned preparation types can be made either in a single piece (*e.g.* a tablet) or in several pieces (*e.g.* granules and pellets). Examples of the numerous patent publications relating to the art
25 include *e.g.* US 4,792,452, US 5,169,638, US 5,593,694, US 5,695,781, and WO 97/25028.

- A requirement for developing a preparation with an appropriate long-
30 term effect is that the drug is absorbed at an at least acceptable rate from the whole gastrointestinal tract, because during the time when the preparation releases the drug, it has already reached to the colon. Most of the drugs presently in use fulfil this requirement. However, there are some drugs which are known to be only absorbed from the stomach
35 and/or the duodenal end of the small intestine (*e.g.* furosemide and nitrendipine). However, retarding the absorption of even these drugs

may be justified for therapeutical reasons, e.g. to eliminate adverse effects due to temporary high drug concentrations. However, using preparations made by techniques of prior art, the release of the drug is retarded so long that the preparation is passed all the way to the ileal
5 end of the small intestine or to the colon. Some drugs also form harmful metabolites, if they have passed to the terminal end of the intestines before their absorption. It is also known that preparations which contain corticoids and anti-inflammatory analgesics (e.g. acetylsalicylic acid, indomethacin, diclofenac, ketoprofen, and ibuprofen) and release the
10 whole dose quickly, tend to irritate the mucous membrane in the stomach. The irritating effect is reduced or eliminated, if the whole dose is not released momentarily but in a retarded manner in the stomach. Similarly, there are drugs which are intended to be locally effective in the stomach, for example drugs for gastric ulcer or substances used for
15 the treatment or the prevention of gastric cancer. Consequently, there are several situations in which it would be possible to utilize pharmaceutical formulations which retard the release of the drug as long as the preparation is in the stomach but, on the other hand, secure that the rest of the dose is released promptly at the duodenal end of the small
20 intestine.

Summary of the invention

The aim of the invention is to present a pharmaceutical formulation
25 whereby the release of a drug can be controlled particularly when the preparation is in the stomach. To achieve this aim, the pharmaceutical formulation according to the invention is primarily characterized in that the polymer is chitosan, and the mixture of chitosan and the drug is in the form of granules or pellets.

30 Chitosan is a generic name for polymers which are produced by N-deacetylation of chitin. Chemically, chitosan is poly[(1-4)-2-amino-2-deoxy- β -D-glucose]. Being a cationic polymer, it dissolves in acidic solutions (e.g. gastric juice), forming a gel. With an increasing ambient
35 pH, its solubility is quickly impaired. The solubility is also dependent on the deacetylation degree and the molecular weight of the chitosan.

Commercially, several types of chitosan are available with varying molecular weight, deacetylation degree and degree of crystallinity. The applicability of chitosan as a pharmaceutical excipient has been the subject of extensive research. Sawayanagi *et al.* (Chem. Pharm. Bull. 30, 2935–2940, 1982) report that chitosan acts as an excellent disintegrant in direct compression tablets. Later, the same researchers presented that chitosan might also be useful for preparing a tablet with a long-term effect from water-soluble drugs, such as propranolol hydrochloride (Chem. Pharm. Bull. 30, 4213–4215, 1982). Kawashima *et al.* showed that acetylsalicylic acid tablets which contained chitosan had a slightly longer term of effect than conventional tablets (Chem. Pharm. Bull. 33, 2107, 1985). US patent 4,738,850 presents that chitosan is complexed with angiotensin converting enzyme (ACE) inhibitors so that a tablet compressed of the mixture forms a gel under both acidic and neutral conditions. However, no experimental evidence of this is presented. Nevertheless, several studies have shown that it is difficult to prepare tablets of mixtures with a high chitosan content (Acatürk, Pharmazie 44, 547, 1989; Nigalaye *et al.*, Drug Devel. Ind. Pharm. 16, 449–467, 1990; Knapczyk, Int. J. Pharm. 89, 1–7, 1993; Sabnis *et al.*, Pharm. Devel. Technol. 2, 243–255, 1997).

Since chitosan only forms a gel in acidic environment (in the stomach), it has also been examined if chitosan can be used in combination with an anionic polymer, wherein the auxiliary polymer would be gelled at higher pH values in the small intestine. This solution has been applied *e.g.* in patents US 5,620,706 and US 4,814,176. Chitosan as an excipient in parallel with chitosan maleate has also been studied in connection with preparing granules with a long-term effect (Henriksen *et al.* Int. J. Pharm. 98, 181–188, 1993). The result was that the release of the model agents was, in fact, retarded by chitosan maleate but, to the contrary, it was accelerated by chitosan. Block and Sabnis (US patent 5,900,408 in 1999) showed that strongly depolymerised chitosan (Mw 3.5 to 75 kD) forms complexes with some drugs, such as cephalosporins. The complex is formed in a dissolved state. The precipitate is purified and dried, after which it can be used for the preparation of *e.g.* tablets showing sustained release of a drug.

Granules and pellets containing chitosan and a drug can be made by known granulation methods. The mixture of the chitosan polymer and the drug must be particularly in the form of granules or pellets, because
5 due to the poor compressibility of chitosan, mixtures containing it are difficult to compress into tablets. Furthermore, the gel-forming rate of granules or pellets is suitably high compared to the gelling of a tablet.

The chitosan used is preferably microcrystalline chitosan, because its
10 granulation/pelletization is easier than that of unmodified chitosan. Moreover, the solubility of the microcrystalline grade is better at pH values close to the neutral. Microcrystalline chitosan is a special form of chitosan which differs from unmodified chitosan with respect to its supermolecular structure. Microcrystalline chitosan is prepared by
15 aggregating glucosamine macromolecules from an acid solution of chitosan by introducing an alkaline solution and stirring strongly, and its preparation methods and properties are disclosed in the art (Journal of Applied Polymer Science, 33, 177-189, 1987; Finnish patent 83426, to which corresponds International publication WO 91/00298).

20 Granules or pellets made of a mixture of chitosan and a drug may also contain other excipients, but the largest component of the excipients, with respect to its content in weight percent, is preferably always microcrystalline chitosan.

25 Chitosan is soluble in acidic solutions, forming a gel whose viscosity is dependent on *e.g.* the content, molecular weight, and deacetylation degree of the chitosan. Particularly the release of acidic drugs from the formed gel is clearly retarded as long as the preparation is in the stom-
30 ach. As the ambient pH rises in the gastrointestinal tract to the values existing in the area of the small intestine (pH 5 to 7), the solubility of the chitosan decreases to such a low level that the gel is dispersed and the rest of the dose is released in a short time.

35 Brief description of the drawings

5

In the following, the invention will be described in more detail with reference to the appended drawings, in which

5 Figs. 1 to 3 show experiments made on different grades of chitosan, and

Fig. 4 shows an absorption test with ibuprofen *in vivo*.

Detailed description of the invention

10

Drug release rates from formulations incorporating microcrystalline chitosan (below MCCh, manufactured by Novasso Oy, Finland) differing in extent of deacetylation (DD %) and molecular weight (Mw) were studied. The effects were evaluated in comparison with an unmodified
15 chitosan (below Ch, manufactured by Primex Ingredients ASA, Norway). Paracetamol and ibuprofen were used as model drugs. The chitosan grades are presented in the following table.

20 Table 1. Deacetylation degree and molecular weight of chitosans studied.

| Grade | Quality | DD % | Mw (kDa) |
|-------|---------|------|----------|
| A | Ch | 90 | 160 |
| B | MCCh | 75 | 25 |
| C | MCCh | 75 | 150 |
| D | MCCh | 90 | 120 |

Mixtures of different ratios of chitosan to drug were granulated using dilute acetic acid (2.5 %). Drug release from granules was studied by
25 means of dissolution tests in USP23 hydrochloric acid buffer, pH 1.2, and phosphate buffer, pH 5.8, using the rotating basket method. Amounts of drug released were determined by spectrophotometry.

The chitosans studied formed gels in the acidic environment (pH 1.2).
30 Under slightly acidic conditions (pH 5.8), however, only MCCh grades with low extents of deacetylation (grades B and C) formed gels. All of

the chitosans retarded dissolution of the model drugs in both buffer solutions. In general, the dissolution profiles best obeyed first-order kinetics. Paracetamol represented a drug that is highly soluble in water, irrespective of pH. It belongs to Class I in the Biopharmaceutical Classification System (BCS). Ibuprofen, which has a low solubility at acidic pH levels, represented Class II drug. The overall effects of the physico-chemical properties of chitosan on the drug release rates were fairly similar for both model drugs, but in ibuprofen formulations the retarding effect was markedly greater. Figure 1 illustrates the effect of Mw of MCCh on dissolution of ibuprofen at pH 5.8. $T_{50\%}$ values ranged from 1.6 ± 0.1 h for grade B to 3.2 ± 0.4 h for grade C. The granules contained 60 % ibuprofen and 40 % microcrystalline chitosan of either grade B or grade C.

When extent of deacetylation degree was constant, increasing Mw markedly retarded the release of ibuprofen. The effect on paracetamol release at the same pH value was minimal. At pH 1.2, however, the retarding effect was moderate. $T_{50\%}$ values were 7.0 ± 0.4 h for grade B and 11.8 ± 1.0 h for grade C.

In contrast to the situation with Mw, the degree of deacetylation of MCCh had no significant effects on drug release. It is possible that an effect can be found within a larger range of the deacetylation degree.

The MCCh grades had markedly greater retarding effects on drug release than unmodified chitosan. This was most clearly evident at pH 5.8 with ibuprofen. $T_{50\%}$ values for unmodified chitosan (A) and MCCh (D) formulations were 2.4 ± 0.3 h and 3.4 ± 0.4 h, respectively. In preliminary tests, solubilities of MCCh have been found to be greater than solubilities of unmodified chitosan above pH 1.2. At pH 5.8, the greater solubility of MCCh could have resulted in efficient formation of gels. Such efficient gel formation could explain the retarding effects of MCCh on drug release.

Figure 2 shows effects of amounts of MCCh grade C on release of paracetamol at pH 1.2. Results with the other two grades, B and D,

were similar. As expected, drug release rates declined as amounts of polymer increased.

Effects of changing amounts of MCCh grade B on drug release from ibuprofen granules at pH 5.8 are shown in Fig. 3. The results with the other two grades, C and D, were in accordance with those shown in Fig. 3. With ibuprofen, in contrast to the effects observed with paracetamol, drug release rate increased as amounts of MCCh were higher.

Description of the preparation

The preparation according to the invention is a multi-part pharmaceutical formulation intended for peroral administration. With respect to its basic starting points, it is a matrix granule or matrix pellet. At first, the drug and the chitosan are mixed with known devices into a homogeneous mechanical powder mixture. Granulation is performed by moistening with a dilute acid solution (e.g. 2.5 % acetic acid), wherein the chitosan also acts as a binder when it is partly dissolved. The mechanical resistance of granules prepared in this way to the movements of the stomach can be improved, if necessary, in two ways. First of all, the granulation can be performed, instead of acetic acid, with a 15–25 % ethanol solution of an enteric polymer, wherein the content of enteric polymer remaining in the granules may be 5–15 %. The enteric polymer may be, for example, a copolymer of methacrylic acid (Eudragit™L or S). The granulation can be performed with known devices, such as a blender granulator or a pelletizing device. After the granulation, the granules with a diameter of 1–2 mm are recovered by sieving, for example the fraction from 1.18 to 1.68 mm. The second way of improving the resistance of the granule containing only the drug and chitosan to the mechanical action of the stomach is to provide them with a porous enteric film. As the film-forming substance, it is possible to use known enteric polymers, such as hydroxypropylmethyl cellulose acetate succinate (Acoat™AS-LF or AS-HF) in such a way that the mass of the formed film is 5 to 10 % of the mass of the whole granule. The coating can be made for example in a fluidized bed granulator. The

ready granules can be divided into dose bags or in hard gelatine capsules. If desired, they can also be compressed into tablets, after the addition of the necessary fillers and other pharmaceutical excipients.

- 5 The invention can be illustrated with the following example compositions. The drug can be any drug which fulfils the conditions set above, *i.e.* it is only absorbed at the initial end of the gastrointestinal tract, it is susceptible of irritating the mucous membrane in the stomach, it forms harmful metabolites at the terminal end of the intestines, or it is only
10 intended to be locally effective in the stomach. The chitosan used in the examples had a deacetylation degree of 75 % and an average molecular weight of 150 kD. The marking q.s. (*quantum satis*) indicates that the granulation solution has been used according to the need, and the solvent has evaporated off in connection with drying of the gran-
15 ules.

Example 1.

| | | |
|----|-------------------|------|
| 20 | Drug | 60 % |
| | Chitosan | 40 % |
| | Acetic acid 2.5 % | q.s. |

Example 2.

| | | |
|----|------------|------|
| 25 | Drug | 60 % |
| | Chitosan | 30 % |
| | Eudragit S | 10 % |
| | Ethanol | q.s. |

30

Example 3.

| | | |
|----|-------------------|------|
| | Drug | 57 % |
| | Chitosan | 38 % |
| 35 | Acetic acid 2.5 % | q.s. |
| | Aquat AS-HF | 5 % |

Water q.s.

The behaviour of the preparation in the stomach and at the duodenal end of the small intestine.

5

When a solid pharmaceutical preparation is orally administered to the patient, it will always stay in the stomach for some time. When taken into an empty stomach, the residence time ranges from 15 minutes to 2 hours. When taken in connection with a meal, the time varies greatly, being about 2 h at its shortest and even more than 10 h at its longest. When staying in the stomach, the chitosan contained in the preparation according to the invention starts to dissolve and forms a gel, thereby preventing a momentary release of the dose. Gel formation will begin even if the granule contained an enteric polymer or a binder, because the gastric juice can penetrate the pores in the granule and dissolve chitosan. This will also take place even if the granule were coated with a porous enteric film. The addition of enteric polymers in small amounts, as presented, does not prevent the release of the drug already in the stomach; it will only retard it. If the granule exits the stomach before all of the drug has been released, the pH close to neutral in the duodenum will quickly result in precipitation of chitosan and dissolution of enteric polymers. Thus, the rest of the drug dose possibly remaining in the preparation is released before the preparation has passed to the jejunum.

15

Figure 4 shows that the preparations according to the invention behave in the above-presented manner in humans. When ibuprofen, used as a model drug in the studies, has been administered as such dosed in a gelatine capsule, the drug is quickly absorbed and the maximum concentration in plasma is achieved in 1.5 to 2 h. If ibuprofen is granulated, according to the invention, with chitosan only, the absorption is clearly retarded, and the maximum concentration is achieved in an average of 3 h. If the granules also contain Eudragit S polymer in addition to chitosan, the time of maximum concentration is shifted even to 4 to 5 h.

15

Claims:

1. A peroral pharmaceutical formulation for controlled release of a drug, containing a mixture of the drug and a polymer for controlling its release, **characterized** in that the polymer is chitosan and the mixture of chitosan and the drug is in the form of granules or pellets.
2. A peroral pharmaceutical formulation according to claim 1, **characterized** in that it is a dosage bag, a gelatine capsule or a compressed tablet containing the granules or pellets.
3. A pharmaceutical formulation according to claim 1 or 2, **characterized** in that the diameter of the granules or pellets is 1 to 2 mm.
4. A pharmaceutical formulation according to any of the preceding claims, **characterized** in that the chitosan content is 20 to 90 wt-%, advantageously 20 to 70 wt-%, preferably 30 to 50 wt-%.
5. A pharmaceutical formulation according to any of the preceding claims, **characterized** in that the chitosan has a molecular weight of 25 to 250 kD, preferably 100 to 150 kD.
6. A pharmaceutical formulation according to any of the preceding claims, **characterized** in that the chitosan has a deacetylation degree of 50 to 95 %, preferably 70 to 90 %.
7. A pharmaceutical formulation according to any of the preceding claims, **characterized** in that the chitosan is microcrystalline chitosan with a high crystallinity degree.
8. A pharmaceutical formulation according to any of the preceding claims, **characterized** in that it contains, in addition to the chitosan and the drug, as a pharmaceutical excipient an enteric polymer, such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose acetate succinate (HPMC-AS), or a methacrylic acid / methyl methacrylate copolymer.

9. A pharmaceutical formulation according to claim 8, **characterized** in that the enteric polymer acts as a binder.
- 5 10. A pharmaceutical formulation according to claim 9, **characterized** in that the enteric polymer is the methacrylic acid / methyl methacrylate copolymer.
- 10 11. A pharmaceutical formulation according to claim 8, **characterized** in that the enteric polymer acts as an agent forming a porous membrane.
- 15 12. A pharmaceutical formulation according to claim 11, **characterized** in that the enteric polymer is the hydroxypropylmethyl cellulose acetate succinate.
- 20 13. A pharmaceutical formulation according to any of the preceding claims 8 to 12, **characterized** in that the content of the enteric polymer is 2 to 20 wt-%, preferably 5 to 10 wt-%.
- 25 14. A pharmaceutical formulation according to any of the preceding claims, **characterized** in that the drug is of a type which is only absorbed from the stomach and/or the duodenal end of the small intestine, such as furosemide or nitrendipine.
- 30 15. A pharmaceutical formulation according to any of the preceding claims 1 to 13, **characterized** in that the drug is of a type which is susceptible of irritating the mucous membrane of the stomach, such as corticoids and anti-inflammatory analgesics, such as acetylsalicylic acid, indomethacin, ketoprofen, diclofenac, or ibuprofen.
- 35 16. A pharmaceutical formulation according to any of the preceding claims 1 to 13, **characterized** in that the drug is of a type which, when passed to the ileal end of the small intestine or the colon without being absorbed, forms harmful metabolites, such as levosimendan.

17. A pharmaceutical formulation according to any of the preceding claims 1 to 13, **characterized** in that the drug is of a type which is locally effective in the stomach, for example a drug for gastric ulcer or a drug used for the treatment or prevention of gastric cancer.

1/2

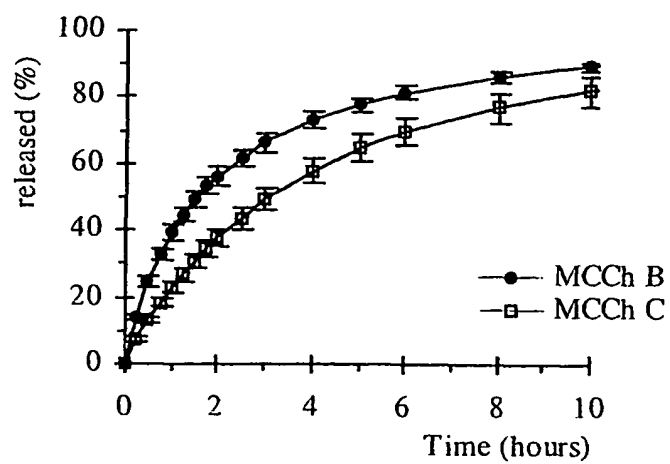


Fig. 1

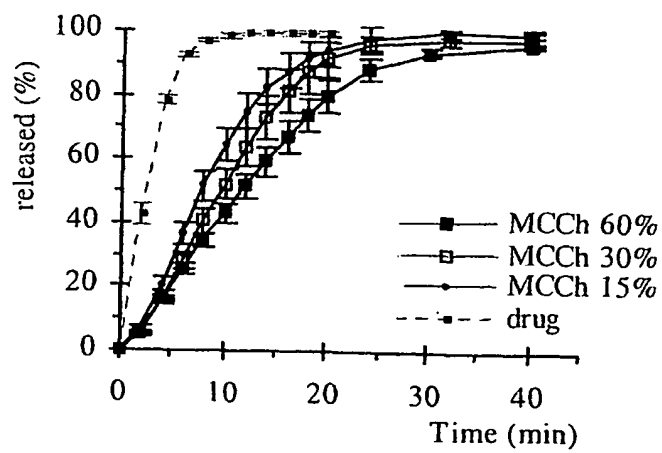


Fig. 2

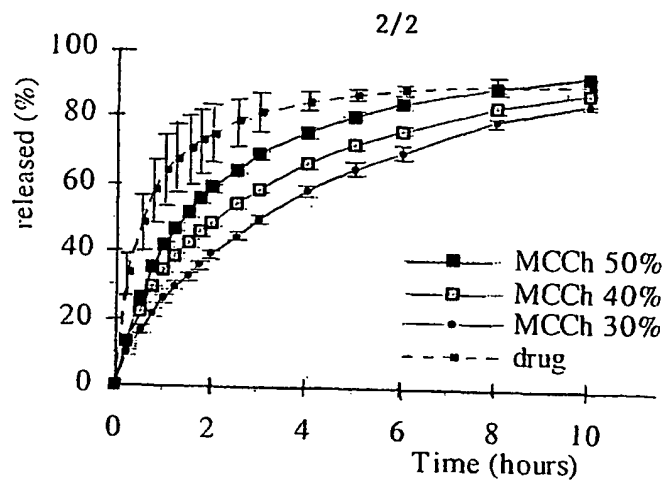


Fig. 3

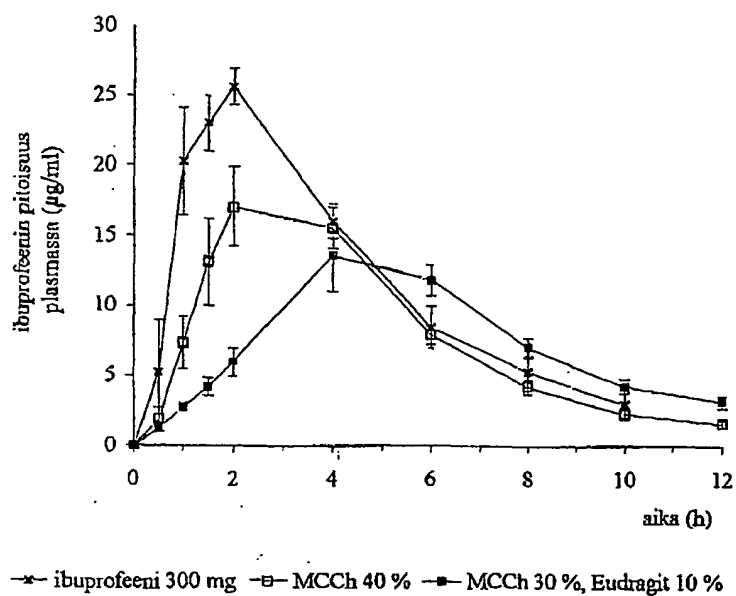


Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 01/00322

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/16, A61K 9/52, A61K 47/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation: to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC INTERNAL, WPI DATA, PAJ, CHEM.ABS.DATA, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| X | US 6030953 A (BAILLY ET AL), 29 February 2000 (29.02.00), column 2, line 10 - line 15, example no.3 and claims nos. 1 and 5 -- | 1-7,14-17 |
| X | EP 0454383 A1 (TEIKOKU SEIYAKU CO., LTD), 30 October 1991 (30.10.91), see example no. 1 and the claims -- | 1-17 |
| A | US 5900408 A (BLOCK ET AL), 4 May 1999 (04.05.99), see example no.1, column no. 8 and the claims -- ----- | 1-17 |

☐

Further documents are listed in the continuation of Box C.

☒

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

9 August 2001

Date of mailing of the international search report

10 -08- 2001

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Carolina Gómez Lagerlöf/BS
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/07/01

International application No.

PCT/FI 01/00322

| Patent document cited in search report | | | Publication date | Patent family member(s) | | Publication date |
|---|---------|----|---------------------|----------------------------|--------------|---------------------|
| US | 6030953 | A | 29/02/00 | AU | 5420599 A | 06/03/00 |
| | | | | BR | 9912979 A | 08/05/01 |
| | | | | EP | 1105123 A | 13/06/01 |
| | | | | WO | 0009123 A | 24/02/00 |
| ----- | | | | | | |
| EP | 0454383 | A1 | 30/10/91 | SE | 0454383 T3 | |
| | | | | AT | 124255 T | 15/07/95 |
| | | | | CA | 2041044 A,C | 24/10/91 |
| | | | | DE | 69110740 D,T | 23/11/95 |
| | | | | DK | 454383 T | 13/11/95 |
| | | | | ES | 2075348 T | 01/10/95 |
| | | | | JP | 2110389 C | 21/11/96 |
| | | | | JP | 4225922 A | 14/08/92 |
| | | | | JP | 8013748 B | 14/02/96 |
| ----- | | | | | | |
| US | 5900408 | A | 04/05/99 | US | 5830883 A | 03/11/98 |
| ----- | | | | | | |